

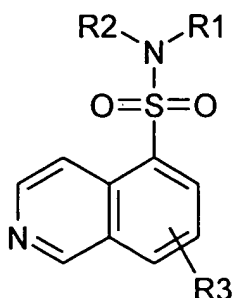
We claim:

1. A method for modulating the growth state of an epithelial cell comprising ectopically contacting the epithelial cell with an amount of an agent effective to alter the rate of proliferation of the epithelial cell, wherein the agent is selected from the group consisting of a hedgehog therapeutic and a ptc therapeutic.
2. A method for modulating the growth state of an epithelial tissue comprising ectopically contacting the tissue with an amount of an agent effective to alter the rate of proliferation of the epithelial cells in the tissue, wherein the agent is selected from the group consisting of a hedgehog therapeutic and a ptc therapeutic.
3. A method for inducing the formation of skin, comprising treating the skin with an amount of an agent effective to induce the formation of new skin tissue, wherein the agent is selected from the group consisting of a hedgehog therapeutic and a ptc therapeutic.
4. A method for inducing growth of hair on an animal, comprising treating the animal with an amount of an agent effective to induce growth of hair, wherein the agent is selected from the group consisting of a hedgehog therapeutic and a ptc therapeutic which induce proliferation of hair follicle keratinocytes.
5. The method of claim 1 or 2, wherein the agent increases the rate of proliferation of epithelial cells.
6. The method of claim 1 or 2, wherein the agent decreases the rate of proliferation of epithelial cells.
7. The method of claim 1 or 2, wherein the epithelial cell is a cutaneous epithelial cell.
8. The method of claim 7, wherein the epithelial cell is a dermal keratinocyte.
9. The method of claim 7, wherein the epithelial cell is a mucosal epithelial cell.
10. The method of claim 7, wherein the epithelial cell is an epithelial stem cell.
11. The method of claim 7, wherein the epithelial cell is a hair follicle stem cell.
12. The method of claim 1, wherein the cell is in culture, and the agent is provided as a cell culture additive.
13. The method of claim 1, wherein the cell is treated in an animal and the agent is administered to the animal as a therapeutic composition.

14. The method of claim 1, wherein the epithelial tissue is in tissue culture, and the agent is provided as a tissue culture additive.
15. The method of claim 1, wherein the epithelial tissue is treated in an animal and the agent is administered to the animal as a therapeutic composition.
- 5 16. The method of claim 3, 4, 13 or 15, wherein the agent is applied topically.
17. The method of claim 1, 2, 3 or 4, wherein the agent is a hedgehog therapeutic.
18. The method of claim 17, wherein the hedgehog therapeutic is a polypeptide including a *hedgehog* polypeptide sequence of at least a bioactive extracellular portion of a hedgehog protein.
- 10 19. The method of claim 18, wherein the polypeptide includes at least 50 amino acids residues of an N-terminal half of the *hedgehog* protein
20. The method of claim 18, wherein the polypeptide includes at least 100 amino acids of an extracellular domain of the hedgehog protein.
21. The method of claim 18, wherein the polypeptide includes at least a portion of the
15 hedgehog protein corresponding to a 19kd fragment of an extracellular domain of the hedgehog protein.
22. The method of claim 18, wherein the hedgehog protein is encoded by a gene of a vertebrate organism.
23. The method of claim 18, wherein the polypeptide includes a *hedgehog* polypeptide
20 sequence represented in the general formula of SEQ ID No. 21.
24. The method of claim 18, wherein the polypeptide includes a *hedgehog* polypeptide sequence represented in the general formula of SEQ ID No. 22.
25. The method of claim 18, wherein the hedgehog protein is encoded by a human *hedgehog* gene.
- 25 26. The method of claim 18, wherein the *hedgehog* polypeptide sequence is at least 60 percent identical to an amino acid sequence of a *hedgehog* protein selected from the group consisting of SEQ ID No:9, SEQ ID No:10, SEQ ID No:11, SEQ ID No:12, SEQ ID No:13, SEQ ID No:14, SEQ ID No:15 and SEQ ID No:16.
- 30 27. The method of claim 26, wherein the *hedgehog* polypeptide sequence is at least 75 percent identical to an amino acid sequence of a *hedgehog* protein selected from the group consisting of SEQ ID No:9, SEQ ID No:10, SEQ ID No:11, SEQ ID No:12, SEQ ID No:13, SEQ ID No:14, SEQ ID No:15 and SEQ ID No:16.

28. The method of claim 26, wherein the *hedgehog* polypeptide sequence is at least 85 percent identical to an amino acid sequence of a *hedgehog* protein selected from the group consisting of SEQ ID No:9, SEQ ID No:10, SEQ ID No:11, SEQ ID No:12, SEQ ID No:13, SEQ ID No:14, SEQ ID No:15 and SEQ ID No:16.
- 5 29. The method of claim 26, wherein the *hedgehog* polypeptide sequence is encodable by a nucleotide sequence which hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID No:1, SEQ ID No:2, SEQ ID No:3, SEQ ID No:4, SEQ ID No:5, SEQ ID No:6, SEQ ID No:7 and SEQ ID No:8.
- 10 30. The method of claim 23, wherein the *hedgehog* polypeptide sequence is an amino acid sequence of a *hedgehog* protein selected from the group consisting of SEQ ID No:9, SEQ ID No:10, SEQ ID No:11, SEQ ID No:12, SEQ ID No:13, SEQ ID No:14, SEQ ID No:15 and SEQ ID No:16.
31. The method of claim 18, wherein the *hedgehog* polypeptide sequence is an amino acid sequence of a Sonic *hedgehog* protein.
- 15 32. The method of claim 18, wherein the *hedgehog* polypeptide sequence is an amino acid sequence of an Indian *hedgehog* protein.
33. The method of claim 18, wherein the *hedgehog* polypeptide sequence is an amino acid sequence of a Desert *hedgehog* protein.
- 20 34. The method of claim 18, wherein the *hedgehog* polypeptide sequence includes an amino acid sequence corresponding approximately to residues 24-193 of SEQ ID No:15.
35. The method of claim 18, wherein the polypeptide is purified to at least 80% by dry weight.
36. The method of claim 18, wherein the polypeptide is a recombinantly produced polypeptide.
37. The method of claim 18, wherein the polypeptide is a chemically synthesized polypeptide.
- 25 38. The method of claim 17, wherein the *hedgehog* therapeutic is a peptidomimetic of a *hedgehog* polypeptide sequence.
39. The method of claim 1, 2, 3 or 4, wherein the agent is a *ptc* therapeutic.
40. The method of claim 39, wherein the *ptc* therapeutic is a small organic molecule which binds to a *patched* protein and derepresses *patched*-mediated inhibition of mitosis.
- 30 41. The method of claims 39, wherein the *ptc* therapeutic binds to *patched* and mimics *hedgehog*-mediated *patched* signal transduction.
42. The method of claim 41, wherein the *ptc* therapeutic is a small organic molecule.

43. The method of claim 41, wherein the binding of the *ptc* therapeutic to *patched* results in upregulation of *patched* and/or *gli* expression.
44. The method of claim 39, wherein the *ptc* therapeutic is a small organic molecule which interacts with epithelial cells to induce *hedgehog*-mediated *patched* signal transduction.
45. The method of claim 44, wherein the *ptc* therapeutic induces *hedgehog*-mediated *patched* signal transduction by altering the localization, protein-protein binding and/or enzymatic activity of an intracellular protein involved in a *patched* signal pathway.
46. The method of claim 39, wherein the *ptc* therapeutic alters the level of expression of a *hedgehog* protein, a *patched* protein or a protein involved in the intracellular signal transduction pathway of *patched*.
47. The method of claim 46, wherein the *ptc* therapeutic is an antisense construct which inhibits the expression of a protein which is involved in the signal transduction pathway of *patched* and the expression of which antagonizes *hedgehog*-mediated signals.
48. The method of claim 47, wherein the antisense construct is an oligonucleotide of about 20-30 nucleotides in length and having a GC content of at least 50 percent.
49. The method of claim 48, wherein the antisense oligonucleotide is selected from the group consisting of: 5'-GTCCTGGCGCCGCGCCGCGCGTCGCC;
5'-TTCCGATGACCGGCCTTTCGCGGTGA; and
5'-GTGCACGGAAAGGTGCAGGCCACACT
50. The method of claims 44, wherein the *ptc* therapeutic is a small organic molecule which binds to *patched* and regulates *patched*-dependent gene expression.
51. The method of claim 44, wherein the *ptc* therapeutic is an inhibitor of protein kinase A (PKA).
52. The method of claim 51, wherein the PKA inhibitor is a 5-isoquinolinesulfonamide
53. The method of claim 51, wherein the PKA inhibitor is represented in the general formula:



wherein,

R_1 and R_2 each can independently represent hydrogen, and as valence and stability permit a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl (such as a carboxyl, an ester, a formate, or a ketone), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_8$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$ -lower alkyl, $-(CH_2)_m-O$ -lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_8$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$ -lower alkyl, $-(CH_2)_m-S$ -lower alkenyl, $-(CH_2)_n-S-(CH_2)_m-R_8$, or

R_1 and R_2 taken together with N form a heterocycle (substituted or unsubstituted);

R_3 is absent or represents one or more substitutions to the isoquinoline ring such as a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl (such as a carboxyl, an ester, a formate, or a ketone), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_8$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$ -lower alkyl, $-(CH_2)_m-O$ -lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_8$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$ -lower alkyl, $-(CH_2)_m-S$ -lower alkenyl, $-(CH_2)_n-S-(CH_2)_m-R_8$;

R_8 represents a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle; and

n and m are independently for each occurrence zero or an integer in the range of 1 to 6.

54. The method of claim 51, wherein the PKA inhibitor is cyclic AMP analog.

55. The method of claim 51, wherein the PKA inhibitor is selected from the group consisting of N-[2-((p-bromocinnamyl)amino)ethyl]-5-isoquinolinesulfonamide, 1-(5-isoquinoline-sulfonyl)-2-methylpiperazine, KT5720, 8-bromo-cAMP, dibutyryl-cAMP and PKA Heat Stable Inhibitor isoform α .

56. A method for promoting the proliferation of skin epithelial cells, comprising ectopically contacting the cells with a polypeptide in an amount effective to increase the rate of proliferation of the epithelial cells, which polypeptide comprises an amino acid sequence including at least a bioactive portion of the N-terminal half of a hedgehog protein.

57. The method of claim 56, which method is used as part of a treatment to control a wound healing process.

58. The method of claim 56, wherein the treatment is selected from a group consisting of burn treatment, skin regeneration, skin grafting, pressure sore treatment, dermal ulcer treatment, post surgery scar reduction and treatment of ulcerative colitis.

59. The method of claim 56, which method is used as part of a treatment of alopecia.

5 60. A method for inhibiting the proliferation of skin epithelial cells, comprising ectopically contacting the cells with agent, in an amount effective to decrease the rate of proliferation of the epithelial cells, which inhibits binding of a hedgehog protein to patched.

61. The method of claim 60, wherein the epithelial cells are hair follicle cells.

62. The method of claim 61, which method inhibits hair growth.

10 63. A preparation of a polypeptide comprising a hedgehog polypeptide sequence including a bioactive fragment of a *hedgehog* protein, which polypeptide is formulated for topical application to epithelial tissue.

64. The preparation of claim 63, wherein the polypeptide is formulated for topical application to skin.

15 65. The preparation of claim 63, wherein the polypeptide includes at least 50 amino acids residues of an N-terminal half of the *hedgehog* protein.

66. The preparation of claim 63, wherein the polypeptide includes at least 100 amino acids of an extracellular domain of the hedgehog protein.

67. The preparation of claim 63, wherein the polypeptide includes at least a portion of the hedgehog protein corresponding to a 19kd fragment of an extracellular domain of the hedgehog protein.

68. The preparation of claim 63, wherein the hedgehog protein is encoded by a gene of a vertebrate organism.

The present application is directed to the discovery that preparations of hedgehog polypeptides can be used to control the formation and/or maintenance of epithelial tissue.

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